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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/748,637	12/30/2003	Nancy L. Brackett	21331/1208887-US1	6890

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EXAMINER	
SCHUBERG, LAURA J	
ART UNIT	PAPER NUMBER
1657	

MAIL DATE	DELIVERY MODE
11/13/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/748,637	BRACKETT ET AL.	
	Examiner	Art Unit	
	LAURA SCHUBERG	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5,6 and 8-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5,6 and 8-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is responsive to papers filed 08/05/2008.

Claim 1 has been amended. No claims have been newly added or canceled.

Claims 1, 3, 5, 6, and 8-19 are currently pending and have been examined on the merits.

Response to Arguments

Applicant's arguments filed 08/05/2008 have been fully considered but they are not persuasive. Applicant's arguments have been addressed in so far as they relate to the new rejections below. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Applicant asserts that the amendment to claim 1 of adding a detection step has rendered the claimed invention allowable.

This is not found persuasive because, upon further review of the prior art, the Examiner has reached the conclusion that the addition of the detection step by the Applicant, while further clarifying the claimed method, does not overcome the overwhelming amount of evidence that suggests the obviousness of the claimed invention. While the detection step was suggested by the Examiner for addition to the claimed method as a missing step that might distinguish over the prior art, an assurance

that this would render the claimed invention allowable was not made by the Examiner in the telephone interview conducted July 28, 2008.

Applicant argues that the link between determining a cytokine profile and treating male infertility was discovered by the Applicants and has not been taught, suggested, or discussed in the literature.

This is not found persuasive because Gruschwitz teaches that patients exhibiting increased levels of specific cytokines TNFα, IL1β, and IL6 showed a significantly reduced amount of progressively motile spermatozoa (page 162 column 2 lines 17-20). These cytokines may result in decreased sperm motility and therefore in reduced ova-penetrating properties (page 162 column 2 lines 42-47). Clearly Gruschwitz required a cytokine profile to detect abnormally high cytokine levels in the semen of infertile men.

Applicant argues that the prior art does not teach or disclose identifying the presence and concentration of individual cytokines and establishing a cytokine profile in a patient sample prior to any treatment. Applicant asserts that none of the cited art provides a link between a cytokine profile and infertility in patients with SCI, for example.

This is not found persuasive because both Gruschwitz and Skurkovich indicate that abnormally high cytokine levels are linked to male infertility. Alexander and Skurkovich teach that high cytokine levels that affect sperm may be treated to reach lower, more normal cytokine levels. Both Brackett et al and Pan et al indicate that elevated levels of the cytokines (specifically TNFα, IL1β, and IL6 as taught by Pan et al) are found in the tissues (specifically semen as taught by Brackett et al) of men with

spinal cord injuries. Brackett et al teach that the cytotoxic cytokine levels in men with spinal cord injuries lead to less motile sperm and infertility. Clearly the detection of abnormally high cytokine levels in a tissue requires a cytokine profile to be ascertained.

Applicant argues that the presence of cytokines was not even discussed in the Brackett et al reference.

This is not found persuasive because Brackett teaches that leukocytospermia is observed in many men with **SCI (spinal cord injury)** and that this condition is thought to contribute to poor semen quality because studies indicate an association with reductions in sperm motility and **loss of sperm function as a result of cytotoxic cytokines** (page 1227 column 1, 2nd paragraph).

Applicant argues that, with regard to the Skurkovich reference, one of ordinary skill in the art would not be motivated to take sperm and pass it over columns and then return it to a patient especially considering the physical attributes of sperm. Applicant asserts that Skurkovich does not teach or disclose obtaining a cytokine profile and determining a specific treatment protocol against cytokines detected.

This is not found persuasive because Skurkovich specifically suggests that the body fluid or tissue sample can be removed from the patient and treated to reduce abnormally high cytokine levels. These abnormally high cytokine levels would inherently require a cytokine profile of normal and abnormal patients to be determined. The suggestion to return the treated tissue to the patient is a general one in situations that would warrant it. Clearly in situations where the treated tissue included sperm (column 12 table 1 as suggested by Skurkovich) the option of using the treated tissue to achieve

its ultimate purpose (i.e. fertility and the fertilization of an egg) would be a desirable option. The cytokines that Skurkovich specifically indicates are responsible for the autoimmune problems are IL-6 and TNF.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 3, 5, 6, 8-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alexander et al (US 6,180,355 B1) in view of Gruschwitz et al (Journal of Andrology 1996), Angelopoulos et al (Fertility and Sterility 1999), Brackett et al (Physical Therapy 1996) and Pan et al (Journal of Neuroscience Research 2002).

Amended claim 1 is now drawn to a method comprising: a) providing from an infertile male subject having a spinal cord injury a biological sample comprising sperm and at least one cytokine selected from a group consisting of TNFα, IL1β, and IL6 ; and b) detecting a cytokine profile in the sample and identifying which of the cytokines are present in the sample in different concentrations as compared to a normal sample; c) contacting the biological sample *in vitro* with an agent that neutralizes the biological activity of the one or more identified cytokines present in the biological sample under conditions that result in increased sperm motility, wherein the sperm having increased motility can be used to impregnate a female subject.

Dependent claims include wherein the male subject has leukocytospermia (claim 3), wherein the sample comprises fluid from the male reproductive tract (claim 5), wherein the sample comprises semen (claim 6), wherein the agent is an antibody that specifically binds to a receptor for the at least one cytokine (claims 8-15) and wherein the agent is a soluble cytokine receptor that specifically binds to the at least one cytokine, TNFα, IL1β, and IL6 (claims 16-19).

Alexander teaches a method that provides for treating men determined to be suffering from a disorder associated with elevated levels of one or more cytokines in one or more components or fractions of semen comprising administering one or more ant-cytokine agents (column 7 line 35). Alexander teaches that compounds that interfere with the production and/or activity of various cytokines are widely known and that such compounds may bind to the cytokine or its receptor, thereby preventing the natural cytokine-receptor interaction (column 7-8). The use of antibodies that specifically bind to the cytokines such as TNFα, IL1β, and IL6 is taught (column 11 line 10) as well as the use of soluble cytokine receptors that bind to the cytokines TNFα, IL1β, and IL6 (column 29, US 5,770,401). Alexander also teaches that various modifications would become apparent to those of skill in the art upon review of reference's disclosure (column 51 lines 8-13).

Alexander does not specifically teach treating male infertility caused by a spinal cord injury by contacting a semen sample that contains cytokines with an agent that inactivates or reduces the activity of the cytokines. Alexander does not teach wherein the subject has a spinal cord injury or leukocytospermia. However, Alexander does teach that the method may be used to treat conditions associated with elevated levels of a cytokine, such as TNFα (column 5 line 12) and that there is a connection between leukospermia and levels of IL-6 (references cited, Shimoya et al).

Gruschwitz teaches that patients exhibiting increased levels of TNFα, IL1β, and IL6 showed a significantly reduced amount of progressively motile spermatozoa (page

162 column 2 lines 17-20). These cytokines may result in decreased sperm motility and therefore in reduced ova-penetrating properties (page 162 column 2 lines 42-47).

Angelopoulos teaches that there are numerous methods known in the art for enhancing sperm motility and that one alternative is applying different types of motility stimulants for intracytoplasmic sperm injection, an infertility treatment (page 240). Angelopoulos also teaches the advantages and disadvantages of the different methods of enhancing sperm motility of a semen specimen (page 243, column 1, 2nd paragraph).

Brackett teaches that leukocytospermia is observed in many men with **SCI (spinal cord injury)** and that this condition is thought to contribute to poor semen quality because studies indicate an association with reductions in sperm motility and **loss of sperm function as a result of cytotoxic cytokines** (page 1227 column 1, 2nd paragraph).

Pan et al teach that detecting a cytokine profile in a sample obtained from a patient with a spinal cord injury shows significantly enhanced levels of TNFα, IL1β, and IL6 (page 320). This amplification of inflammatory signaling is indicated to lead to both edema, producing ischemia and secondary cell death, and recruitment of peripheral lymphocytes, initiating phagocytosis of damaged tissues (page 321-322).

One of ordinary skill in the art would have been motivated to use the method of Alexander as a treatment for infertile males because Gruschwitz teaches a connection between patients with increased levels of TNFα, IL1β, and IL6 and reduced sperm motility (page 162 column 2 lines 17-20), Pan et al teach a connection between elevated levels of TNFα, IL1β, and IL6 and patients with spinal cord injuries and

because the method of Alexander provides for treating men determined to be suffering from a disorder associated with elevated levels of one or more cytokines in one or more components or fractions of semen comprising administering one or more anti-cytokine agents (column 7 line 35). One of ordinary skill in the art would have been motivated to use the method of Alexander directly on semen samples that had a cytokine profile that would benefit from reducing cytokines known to interfere with sperm motility, such as in intracytoplasmic sperm injection (ISCI-which is a treatment for male infertility) because Angelopoulos teaches that ISCI benefits from enhancement of sperm motility and that there are several alternatives for accomplishing this (page 240) and because Gruschwitz teaches that patients exhibiting increased levels of TNFα, IL1β, and IL6 showed a significantly reduced amount of progressively motile spermatozoa. In addition, treatment of a sperm sample would be an obvious alternative to directly injecting the agent into the patient (such as taught by Alexander) where fertilization was to be accomplished by alternative methods that require collection of the semen sample prior to fertilization (such as ISCI). One of ordinary skill in the art would have had a reasonable expectation of success because Alexander teaches that compounds that interfere with the production and/or activity of various cytokines are widely known and that such compounds may bind to the cytokine or its receptor, thereby preventing the natural cytokine-receptor interaction (column 7-8).

One of ordinary skill in the art would have been motivated to use the method of Alexander to treat men with SCI and leukocytospermia because Alexander teaches that the method can be used to treat conditions associated with elevated levels of a cytokine

(column 5 line 12) and Brackett and Pan et al teach that men with SCI and leukocytospermia have cytotoxic levels of cytokines (p.1227). In addition, treatment of a sperm sample would be an obvious alternative to directly injecting the agent into the patient (such as taught by Alexander) where fertilization was to be accomplished by alternative methods that require collection of the semen sample prior to fertilization (such as with spinal cord injured patients). One of ordinary skill in the art would have had a reasonable expectation of success because Alexander teaches the use of anti-cytokine compounds for IL-6 and also that there is a connection between IL-6 and leukospermia (also known as leukocytospermia).

Therefore, the combined teachings of Alexander, Gruschwitz, Angelopoulos, Brackett and Pan et al render obvious Applicant's invention as claimed.

Claims 1, 3, 5, 6, 8-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Skurkovich et al (US 5,888,511) in view of Brackett et al (Physical Therapy 1996), Gruschwitz et al (Journal of Andrology 1996) and Alexander et al (US 6,180,355 B1).

Skurkovich teaches a method for treating an autoimmune disease by extracorporeal (outside the body and interpreted as *in vitro*) exposure of the patient's fluid to an immunosorbent comprising autoimmune inhibitor (such as anti-IL-6 and anti-TNF antibodies as well as antibodies to TNF receptor), followed by the return of the treated fluid to the patient (column 5 lines 40-67). The term autoimmune inhibitor is

used to refer to a compound which binds to or neutralizes hyperproduced cytokines (column 10 lines 55-64). Male infertility is indicated as an autoimmune disease to be treated by this method and sperm is indicated as the tissue affected (column 12, table 1).

Skurkovich does not specifically teach wherein the infertile male subject has a spinal cord injury or leukocytospermia.

Brackett teaches that leukocytospermia is observed in many men with SCI and that this condition is thought to contribute to poor semen quality because studies indicate an association with reductions in sperm motility and **loss of sperm function as a result of cytotoxic cytokines** (page 1227 column 1, 2nd paragraph).

Gruschwitz teaches that patients exhibiting increased levels of TNFα, IL1β, and IL6 showed a significantly reduced amount of progressively motile spermatozoa (page 162 column 2 lines 17-20). These cytokines may result in decreased sperm motility and therefore in reduced ova-penetrating properties (page 162 column 2 lines 42-47).

Alexander teaches a method that provides for treating men determined to be suffering from a disorder associated with elevated levels of one or more cytokines in one or more components or fractions of semen comprising administering one or more ant-cytokine agents (column 7 line 35). Alexander teaches that compounds that interfere with the production and/or activity of various cytokines are widely known and that such compounds may bind to the cytokine or its receptor, thereby preventing the natural cytokine-receptor interaction (column 7-8). The use of antibodies that specifically bind to the cytokines such as TNFα, IL1β, and IL6 is taught (column 11 line 10) as well

as the use of soluble cytokine receptors that bind to the cytokines TNFα, IL1β, and IL6 (column 29, US 5,770,401). Alexander also teaches that various modifications would become apparent to those of skill in the art upon review of reference's disclosure (column 51 lines 8-13).

Pan et al teach that detecting a cytokine profile in a sample obtained from a patient with a spinal cord injury shows significantly enhanced levels of TNFα, IL1β, and IL6 (page 320). This amplification of inflammatory signaling is indicated to lead to both edema, producing ischemia and secondary cell death, and recruitment of peripheral lymphocytes, initiating phagocytosis of damaged tissues (page 321-322).

Therefore, one of ordinary skill in the art would have been motivated to apply the method of Skurkovich to infertile male subjects with spinal cord injuries and leukocytospermia because Brackett and Pan et al teach that these subjects suffer from cytotoxic cytokines (hyperproduced cytokines), specifically those cytokines that have been known to affect sperm motility as taught by Gruschwitz. One of ordinary skill in the art would have been motivated to use semen as the type of sample used since this is fluid where sperm are located. One of ordinary skill in the art would have had a reasonable expectation of success because Skurkovich suggests that male infertility is a condition that can be treated and that the tissue type affected was sperm.

One of ordinary skill in the art would have been motivated use the method of Skurkovich directly on semen samples that had an abnormally high cytokine profile that would benefit from reducing cytokines known to interfere with sperm motility because Gruschwitz teaches that male patients exhibiting increased levels of TNFα, IL1β, and

IL6 in their semen showed a significantly reduced amount of progressively motile spermatozoa. One of ordinary skill in the art would have had a reasonable expectation of success because Alexander teaches that using anti-cytokine therapy to reduce toxic cytokine levels detected in semen samples is known in the art.

One of ordinary skill in the art would have been motivated to include anti-IL1β as well as anti-IL-6 and anti-TNF antibodies and antibodies to TNF receptor as the autoimmune inhibitors in the method of Skurkovich because Gruschwitz teaches that patients exhibiting increased levels of TNFα, IL1β, and IL6 showed a significantly reduced amount of progressively motile sperm. One of ordinary skill in the art would have had a reasonable expectation of success because Skurkovich teaches that additional interleukin antibodies can be used as well (column 5 lines 32-52).

Therefore the combined teachings of Skurkovich, Brackett, Gruschwitz, Alexander and Pan et al render obvious Applicant's invention as claimed.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAURA SCHUBERG whose telephone number is (571)272-3347. The examiner can normally be reached on Mon-Fri 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leon B Lankford/
Primary Examiner, Art Unit 1651

Laura Schuberg